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Rational and design of EuroCRT: an international observational study on multi-modality imaging and cardiac resynchronization therapy.

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Abstract:

Assessment of left ventricular (LV) volumes and ejection fraction (LVEF) with cardiac imaging is important in the selection of patients for cardiac resynchronization therapy (CRT). Several observational studies have explored the role of imaging-derived LV dyssynchrony parameters to predict the response to CRT, but have yielded inconsistent results, precluding the inclusion of imaging-derived LV dyssynchrony parameters in current guidelines for selection of patients for CRT. The EuroCRT is a large European multicentre prospective observational study led by the European Association of Cardiovascular Imaging (EACVI). We aim to explore if combing the value of Cardiac magnetic resonance (CMR) and echocardiography could be beneficial for selecting heart failure patients for CRT in terms of improvement in long-term survival, clinical symptoms, LV function and volumes. Speckle tracking echocardiography will be used to assess LV dyssynchrony and wasted cardiac work whereas myocardial scar will be assessed with late gadolinium contrast enhanced CMR. All data will be measured in core laboratories. The study will be conducted in European centres with known expertise in both CRT and multimodality cardiac imaging.

Keywords: cardiac resynchronization therapy, cardiac magnetic resonance,echocardiography, strain, observational study.

Introduction

The potential role of cardiac imaging to identify which patients with heart failure benefit from cardiac resynchronization therapy (CRT) has been assessed in several studies (1-6). Echocardiography is used to assess left ventricular ejection fraction (LVEF) and volumes according to current guidelines, but echocardiographic measures of cardiac dyssynchrony were considered not sufficiently validated and robust to be implemented in the current guidelines (7). Echocardiographic parameters have mostly been tested in single-centre studies with small cohorts and often in retrospective studies (8-10). The prospective observational PROSPECT trial showed that the initially proposed echocardiographic parameters of cardiac dyssynchrony had a modest accuracy to predict response to CRT (8). Subsequent studies have shown that speckle tracking echocardiography may be a better tool to reliably measure LV dyssynchrony (1, 11-13). In the normal heart, all LV segments contract in a relatively synchronized fashion and contribute to blood ejection into the aorta. When there is electrical conduction delay, however, early and late activated segments contract at different times and energy might be wasted in stretching opposing segments (12, 14-16). As observed typically in patients with left bundle branch block (LBBB), the early-activated septum contracts prior to aortic valve opening and stretches the LV lateral wall, and contraction in the late activated lateral wall causes a variable degree of systolic lengthening of the septum(1, 17, 18). The negative work during systolic lengthening makes no contribution to LV ejection, and therefore represents a waste. It has been suggested that the amount of effective (positive) work remaining in the dyssynchronous ventricle reflects the potential for recovery of function after CRT (15, 16, 19). LV pressure-strain loops (PSLs) are a novel

and reliable tool for the non-invasive assessment of myocardial work (15, 16, 20). Furthermore, the use of cardiovascular magnetic resonance (CMR) in particular with late gadolinium enhancement (LGE), permits the assessment of myocardial scar which has been associated with poor response to CRT (21-23). The combination of LV dyssynchrony assessment with speckle tracking echocardiography and myocardial scar assessment with CMR has shown better accuracy to identify patients who will benefit from CRT (21, 24, 25). However, these single-center studies included only small cohorts of patients and dyssynchrony was not extensively evaluated.

Therefore, we propose an European international observational study (EuroCRT) to determine the role of multimodality imaging to identify heart failure patients who will benefit from CRT. The objectives of the present study are as follows:

- To explore the combined value of LV mechanical dyssynchrony and wasted cardiac work measured with speckle tracking echocardiography and of myocardial scar measured with LGE-CMR to accurately identify patients who will benefit from CRT.
- To test the robustness of this combined approach.

The results of this observational study will constitute a step forward to proposing a new prospective randomized study.

Methods

The EuroCRT survey will be conducted in high volume centres with specific expertise in the evaluation and treatment of heart failure patients who are candidates for CRT and

will be led by the ‘Research and Innovation’ Committee of the European Association of Cardiovascular Imaging (EACVI) and the European Heart Rhythm Association (EHRA). The selected centres will be involved in a 12-month inclusion period followed by a 6-month follow-up period. Institutional ethical approval will be requested in each centre according to the local regulations complying with the principles outlined in the Declaration of Helsinki for research in human subjects. Patients should be treated according to the routine practice of each centre. The implantation of the CRT should not be influenced by the data collected.

Study population

Inclusion criteria: patients who are listed on clinical grounds for CRT implantation according to the current European Society of Cardiology guidelines(6), and will consent to the study. They will be evaluated before and 6 months after implantation. Patients undergoing upgrades of pacemaker or implantable cardiac defibrillator will also be included.

Exclusion criteria: inappropriate echocardiographic image quality according to the judgment of the investigator; absence of echocardiographic follow-up at 6 months; absence of an indication for CRT according to the current guidelines; general contraindication for CMR (including metallic cerebral clips, non-MR conditional devices) and severe renal dysfunction (eGFR<30 ml/min/1.73m^2). Patients in atrial fibrillation will also be excluded.

Protocol (Figure 1): The baseline evaluation includes clinical evaluation (NYHA functional class, 6-minute walking distance and quality of life), laboratory testing (with

specific focus on NT-pro brain natriuretic peptide determination), electrocardiographic (ECG) recording, echocardiographic and CMR evaluation of cardiac dimensions and function. These investigations will be repeated at 6 months' follow-up. CMR will be repeated at 6 months in patients receiving a CMR-conditional or compatible device.

Clinical information including cardiovascular risk factors, ECG and biological marker (creatinine, haemoglobin, sodium, NT-proBNP) will be collected (Table 1). The ECG will be analysed and rhythm, PR interval duration, QRS axis, duration and morphology will be recorded according to guidelines (26).

Before implantation of the CRT device, patients will be imaged by transthoracic echocardiography according to a predefined acquisition protocol (Table 2) (27, 28) using the same ultrasound platform (ViVid E9, S70 or E95, General Electric Healthcare, Horten, Norway). During echocardiography, the ECG-trace recording will be carefully optimized to ensure good visualization of the QRS onset throughout the echocardiographic assessment. The frame rate of the images should be 50-90 Hz. The image quality should be optimized to get the best visualization of the endocardial and epicardial borders. At least 3 cardiac cycles will be acquired. In addition to conventional grey scale images, contrast agents for cavity opacification will be allowed when needed to obtain optimal determination of LV volumes and LVEF. Echocardiography will be interpreted on site, the exam will be centralized using a web-platform (ASCENT: automated anonymization, and the same recording parameters with a specific password for each co-investigator), and a centralized analysis (Inserm 1414 Clinical Investigation Center, Innovative Technology, Rennes, F-35000) will be performed.

CMR will be performed before device implantation using standard CMR scanners (1.5 and 3T) with cardiac software. In patients who undergo implantation of an MR-conditional CRT device, CMR will be repeated at 6-month post-implantation. All CMR studies will be performed according to a predefined CMR acquisition protocol detailed below, and all anonymized data will be sent and analysed by the Bristol CMR Unit core-lab. Images will be analysed by an expert operator ESC CMR level III certified using a commercially available software (CMR42, Circle Cardiovascular Imaging, Calgary, Canada).

CRT-procedure will be performed as per local standard operating procedures. The post-implant period will be managed according to the local procedures in each centre.

Study end-points. At 12 -month, the primary endpoint will be a reduction in left ventricular end-systolic volume of ≥15% (i.e. LV reverse remodelling).

The secondary endpoint will be will be the heart failure clinical composite response (29, 30). The composite endpoint was developed by Milton Packer(29) at 12-month, This is a combined endpoint (QoL, NYHA-class, hospitalization for heart failure and death) that has been extensively been used(31).

Furthermore, event rates for death, hospitalisation for any cardiovascular reason and the clinical improvement (as assessed with the NYHA functional class, the 6 minutes walking test distance and the improvement in quality of life according to questionnaires used in the Milton Packer score) (29) will be recorded.

Echocardiographic data analysis

A complete echocardiography including Global longitudinal strain (GLS) will be performed and recorded for a core laboratory analysis. Left atrial (LA) volume, right ventricular (RV) size and function will be recorded according to recommendation (including RV strain free wall) (27, 32)

Assessment of dyssynchrony

Mechanical dyssynchrony will be quantified using a multi-parametric approach (table 2). Intra-ventricular dyssynchrony will be defined by: the presence of septal flash (33) and/or apical rocking (34). These two parameters have been previously described and will be assessed qualitatively(34, 35). Septal flash is a premature and short contraction of the septum during the QRS and then before the aortic valve opening. Apical rocking is a displacement or the LV-apex towards the lateral wall.

Systolic mechanical dispersion will be quantified according to the methodology previously proposed(36).

In addition to these 2 approaches, Mitral inflow pattern, Mitral inflow duration will be measured(37). The pattern of LV-septum deformation will be analyzed according to Marechaux et al(38).

Quantification of cardiac work

Cardiac work will be calculated as a function of time throughout the cardiac cycle from the time-strain curve recordings and the estimated LV pressure. Peak systolic LV pressure will be assumed to be equal to peak arterial pressure measured with cuff manometer, as the average of three recordings. Cardiac work will be assessed by calculating the rate of segmental shortening (strain rate) by differentiation of the strain

curve and multiplying this with instantaneous LV-pressure. This product is a measure of instantaneous power, which will be integrated over time to give work as a function of time in systole, defined as the time interval from mitral valve closure to mitral valve opening. Two-dimensional imaging of mitral and aortic valves in parasternal long-axis (PLAX) view will be used to define timing of opening and closure of the mitral and aortic valves(16, 20, 39, 40).

During the LV ejection period, work performed during segmental elongation represents energy loss, defined as negative work (NegW). Work performed during segmental shortening represented positive work (PosW). During isovolumetric relaxation, this is reversed so that work during shortening is considered negative work and work during lengthening is considered positive work. Work efficiency (WE) is defined as PosW / (PosW + NegW) x 100. Global positive, negative and work efficiency will be reported as the mean values of all LV segments (figure 2).

Cardiac Magnetic Resonance Imaging (Figure 3)

The CMR protocol includes standard long- axis views (3-, 2- and 4-chamber views) followed by a full stack of continuous short-axis cine encompassing the LV/RV from base to apex using a breath-hold steady-state free precession (SSFP) cine technique. LGE-CMR imaging will be performed in the same short- and long-axis cine orientation 10-15 min after administration of 0.1 to 0.2 mmol/kg of gadolinium-chelate contrast agent. Images will be acquired using an inversion recovery prepared breath-hold gradient-echo technique (IR-GRE) following a Lock-Locker TI shout sequence for the identification of the optimal starting TI value to null the signal in the normal myocardium. The inversion time will be progressively optimized to null normal myocardium (typical values, 250–350 ms).

Each slice will be obtained during a breath-hold of 10 to 15s depending on the patient's heart rate.

The parameters measured will be LV and RV volumes and ejection fraction. LV fibrosis will be measured using the full-width-half-maximum (FWHM) method of the tissue characterization module, and expressed both in grams and in % of the LV mass, as previously described(41). The location and numbers of myocardial segments affected by LGE will be recorded; the transmural extent of LGE will visually assessed per segment using a 0-4 score (0=no LGE, 1=0-25% LGE, 2=26-50% LGE, 3= 51-75% LGE, 4=≥75% LGE) and quantify also.

LV global longitudinal strain (GLS) will be measured from two long-axis cine images using feature-tracking analyses module.

Statistical analysis

The baseline demographic, clinical, echocardiographic and CMR characteristics will be compared between patients who have met the primary end-point and those remaining free from end-points at 12-month. Similar comparison and description will be performed according to secondary end-points.

After the normality of the distribution is assessed using the Kolmogorov-Smirnov test, all baseline continuous variables will be compared between the 2 groups for statistically significant differences using Student's t-test or the Mann-Whitney test, as appropriate. Categorical variables will be compared using the Chi^2 test or Fisher's exact test. The independent determinant of CRT response will be assessed using logistic regression. Firstly, univariate analyses will be performed, and odds ratios and 95% of confidence

intervals (CI) will be reported. Secondly, all univariate variables with a p-value <0.10 will be included in a backward stepwise model. Special care will be maintained to avoid collinearity among the included variables. In this regard, variables with a high degree of collinearity will be selected according to the best univariate p value. Final variables identified as independently associated with the CRT-response will be confronted to the previously established predictive score (i.e., the Bernard et al. score(42)). According to the current literature and our experience, we anticipate including up to 6 variables (with low collinearity) from the dyssynchrony analysis and CMR parameters in the logistic regression model aiming to identify the independent determinants of non-response.

From the literature, the expected response rate to CRT is 70%. According to the main secondary endpoint (reduction in LVESV of at least 15%) the rate response is 50% in the SEPTAL CRT trial, resulting in 50 to 40% of patients potentially non-responders, according to the LV reverse remodelling criteria (43). Consequently, using a ratio of 10 non-responders for each selected variable, a minimal number of 70 non-responders are needed to appropriately answer the primary objective of the observational study. This results in a calculated total sample size of 234 for an expected non-response rate of 30%. We aim to recruit 250 patients to account for missing data or loss of follow-up.

Discussion

Imaging modalities have been tested previously and have not met the clinical expectations in improving the selection of candidates for CRT(8, 44, 45). Nevertheless, new evidence on the role of imaging to select patients for CRT is encouraging (34, 46-

48). In particular, modern multi-modality imaging approaches have the potential to improve the selection of candidates for CRT (Table 4). From previous studies(21, 25), it has been shown that the presence of myocardial scar is an important determinant of response to CRT. However, its integration in a multi-parametric approach to select patients for CRT has not been evaluated in large prospective multi-centre studies using dedicated core labs for ultrasound and CMR studies.

By using echocardiography, new approaches for quantifying the mechanical dyssynchrony have been proposed (33). There are also issues that are not completely resolved like the relevance of right ventricular function, of secondary mitral regurgitation or left atrial size(49-51). Mechanical dispersion is also something that remains to be explored in a large series of patients treated by CRT(36). Mechanical dyssynchrony parameters can nowadays be quite automatically computed and are taking advantage of the past studies and a better understanding of the pathophysiology(52). The strain delay index has been proposed and tested in the multicentre MUSIC-trial involving 235 patients treated by CRT. The results were clearly encouraging (12). There are important results published with the cardiac work indices obtained by computing longitudinal strain curves(53). In EuroCRT, we will consider an approach combining the timing and the amount of segmental deformation using the cardiac work indices previously described (16, 20). In addition, the septal flash and apical rocking are two semi-quantitative approaches that are easy to apply and to test (33, 54, 55). These simple approaches have been tested and validated in some studies but their relative value with respect to the quantitative assessment of the cardiac wasted work has not been tested in any large multicentre study. It has been decided to use only one sort of echo-machine to increase

to robustness. In addition, the centralized reviewing of the images will be extremely useful to assess the relative reproducibility of the “automatically” calculated parameters extracted from strain curves against the variability of the septal flash and the apical rocking (ie comparing corelab versus individual labs involved in EuroCRT)(34).

Conclusion

EuroCRT will be the first large multi-centre European prospective observational international study to test the role of CMR and modern echocardiographic-updated parameters to predict the response to CRT among patients implanted according to the current guidelines.

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Figures legend

Figure 1: global presentation of the observational study

Figure 2: presentation of the impact of mechanical dyssynchrony on longitudinal strain curves: in blue: the septum with a too early contraction; in red the lateral wall with a delayed contraction.

GLS: global longitudinal strain; TTP: time to peak; WE: wasted energy

Figure 3: example of the quantification of the late gadolinium enhancement

Table 1: Clinical parameters to be recorded

Parameters	Before implantation	6-month follow-up
Age	+	+
Body mass index	+	+
Systolic blood pressure	+	+
Diastolic blood pressure	+	+
Heart rate	+	+
NYHA-class	+	+
6-minute walk test distance	+	+
Creatinine (micromole/l)	+	+
Haemoglobin (g/dl)	+	+
NT-proBNP (pg/ml)	+	+
ACEI/Sartan-dosage/day	+	+
Beta-blocker dosage/day	+	+
Diuretic dosage/day	+	+
MRA dosage/day	+	+
Ischaemicaetiology (Y/N)	+	+
Heart failure decompensation(Y/N before implant and during the 6-months of follow-up)	+	+

Table 2: Echocardiographic parameters or loops that will be mandatory for the analysis or corelab analysis

Parameters /loops	Before implantation	6-month follow-up
Apical 4-, 2-, 3-ch.views showing LV and LA (3 beats)	+	+
Apical 4-, 2-, 3-ch.view with colour Doppler on valves	+	+
Dedicated loops on the RV in 4-ch.view	+	+
Mitral inflow (E, A, E-DT)	+	+
LVOT VTI (cm)	+	+
e' (septal & lateral) (cm/s)	+	+
s' (septal & lateral) (cm/s)	+	+
TR velocity (m/s)	+	+
RVs' (cm/s)	+	+
LV EF (%)	+	+
GLS (%)	+	+
LVEDD (mm)(parasternal long-axis view)	+	+
LVESD (mm)(parasternal long axis view)	+	+

IVS and PW thickness (mm) (parasternal long-axis view	+	+
Parasternal long-axis view loop (3 beats)	+	+
Parsternal short-axis view at the level of papillary muscle	+	+
RV outflow tract VTI(cm)	+	+
Inferior vena cava loops (3 beats)	+	+
Optional: 4D volumetric acquisition of the LV over 4 to 6 beats	+	+
Apical 4-Ch. View colour DTI highest frame rate loop (> 2 beats)	+	+

Table 3: Key imaging parameters that will be examined for their ability to predict the response to CRT

Parameters /loops	Before implantation	6-month follow-up
Localization: amount of LGE	+	
LV volumes and diameters	+	+
Septal flash	+	+
Apical rocking	+	+
Pattern of LV longitudinal strain(38)	+	+
Cardiac work indices	+	+
Strain delay indices (cardiac work, dispersion,)	+	+
LA volumes and deformations	+	+
Right ventricular function indices (TAPSE)	+	+
LV Mechanical dispersion	+	+

Table 4

	PROSPECT [10]	RethinQ[26]	Echo CRT [27]	Euro-CRT objectives
Population	286 out of 498 enrolled	80 out of 172 enrolled	809 out of 1680	250
LVEF (%)	23.6 ± 7.0	26 ± 6	27.0 ± 5.4	≤ 35%
QRS-duration (ms)	163 ± 22	106± 13	105 ± 12	>120
Follow-up (months)	6	6	19.4	6
LV end-diastolic	Volume 230 ± 99 ml	Volume 210 ± 75 ml	Diameter 66.1 ± 7.4 mm	unknown
Use of time to peak indices in tissue Doppler imaging	**+**	**+**	**-**	**-**
Use of longitudinal strain	**-**	**-**	**-**	**+**
Use of patterns of LV-regional function and dyssynchrony	**-**	**-**	**-**	**+**
Use of indices of regional LV myocardial function	**-**	**-**	**-**	**+**
Use of radial strain	**-**	**-**	**+**	**+**
Use of M-mode	**+**	**+**	**-**	**+**
Use of pulse Doppler indices of dyssynchrony	**+**	**+**	**-**	**+**
Use of any parameter of right ventricular function or pressure	**-**	**-**	**-**	**+**
Use of CMR	**-**	**-**	**-**	**+**
Result in term of interest of imaging indices	**-**	**-**	**-**	**unknown**